## I. **REMARKS**

### A. Status of Claims

Claims 4, 7-9, 11, 13-16, 35-36, 40-42, 59-60, 71-89, 90-94, and 96-98 are pending in this Application according to Applicant's count. This listing differs from the listing of the pending claims made by Examiner in the Action dated 05-21-2009. Examiner is respectfully requested to confirm the listing of the claims pending in the application against her previous listing and that of Applicant herein. The following claims have been cancelled from this Application: 1-3, 5-6, 10, 12, 17-33, 34, 37-38, 39, 43-54, 55, 56-57, 58, 61-70, and 95.

Claims 15, 16, and 71 are amended herein to correct minor matters of form and the amendments are not substantive in nature.

### B. Extension of Time

Accompanying this Response is a Petition for Extension of Time (PTO/SB/22) for a 1-month extension of time as well as the required fee.

## II. **REJECTION UNDER 35 USC §103(A)**

### A. Section 103(a) Rejection

The claims pending in this Application are rejected as obvious under 35 USC §103(a) over Coffee (WO 98/03267) in view of Liu et al (US 6,465,009) and Murray et al (US 6,709,669).

Examiner contends that it would have been obvious to the skilled artisan at the time Applicant's invention was made to incorporate a water soluble polymer such as vinylpyrrolidone-vinyl acetate copolymer and fish gelatin as a binder into Coffee's method. The person of ordinary skill would have been motivated to make these modifications because vinylpyrrolidone-vinyl acetate copolymer and fish gelatin would assist in making tablets with (i) better resistance to moisture and (ii) have adequate

hardness. The skilled artisan would reasonably have expected success because Coffee and Liu and Murray teach a "process of manufacturing tablets that can be used in the same field of endeavor, i.e., a process that produces tablets that are advantageously hard, and dissolve rapidly in the oral cavity upon contact with saliva.

B. The References

1. The Coffee Reference

The Coffee reference teaches a process for manufacture of a wound dressing using electrohydrodynamic aerosolization (spraying) means where the wound dressing is formed of a biocompatible water soluble polymer which must additionally be biodegradable or bioresorbable. The wound dressing may be directly applied to the wound using a hand-held EHD means.

The polymers described by Coffee which fit the requirements of being biocompatible, i.e. non-toxic or non-allergenic to the human or animal patient and which must also be biodegradable or bioresorbable are as follows:

| | |
|---|---|
| Polyhydroxybutyric acid | Polyglycolic acid |
| Polyvinyl alcohol | Polylactic acid |
| New Skin® | Polyurethane<br>(produces a foam rather than mat) |

The wound dressing of Coffee may contain an active ingredient which is deposited on the individual fibres of the mat, or situated in the gaps between fibres or surrounded by the polymer fibre.

In the invention taught by Coffee, rapid-release or rapid dissolution of the wound dressing is not a desirable feature because the whole purpose of the wound dressing is to form a barrier to entry of harmful material like bacterial but allow the entry of air and the exit of blood and pus as the wound heals. The wound dressing of the Coffee invention is designed to remain in place for a reasonable period of time

measured in at least hours, if not several days. The wound dressing may contain an active ingredient, e.g., an antibiotic; however, the active agent will release slowly to the wound as the wound dressing biodegrades or bioresorbs. A wound dressing that dissolved in 60 seconds or less would be useless.

Coffee allows for the use of organic solvents to dissolve the polymer and/or an active ingredient. If the active agent is not soluble in aqueous liquids the polymer and/or the active agent may be dissolved in a suitable solvent, e.g., methanol, propanol, methylene chloride, acetone and chloroform. As long as the solvent is sufficiently volatile to evaporate as the mat of fibers is formed, organic solvents may be used in the EHD process taught by Coffee.

2. The Liu Reference

The Liu et al reference teaches the preparation of a rapidly dissolving compressed tablet formed from a non-saccharide, water soluble polymer that rapidly disintegrates. As taught by Liu, it was known in the art that rapid dissolution and strong tablets were mutually exclusive qualities. If the skilled artisan obtained rapid dissolution, the skilled artisan also obtained a soft, friable tablet that could not withstand the stresses caused by packaging, handling and shipping (Col 1, lines 37-44). Liu overcomes the problems associated with the formulation of a rapid dissolution tablet by use of certain polymers. In addition to producing a strong, rapidly dissolving tablet, another of Liu's aims was to do so without the use of organic solvents.

The basic process for manufacture of the tablets of Liu comprises:

(1) granulation of the active agent and the polymer;

(2) compression of the granulate;

(3) humidification of the compressed tablets in a 50% to 100% relative humidity chamber; and

(4) drying of the tablet until the desired hardness is achieved.

Water soluble polymers that are taught as being suitable for use in the Liu invention are shown below.

| | |
|---|---|
| Polyvinylpyrrolidone (PVP) and substituted PVPs, e.g., N-vinyl-pyrrolidone, etc. (Col. 2, lines 19-26) | Hydroxypropyl methyl cellulose |
| Polyethylene glycol | Hydroxy ethyl cellulose |
| Sodium alginate | |
| Hydroxypropyl cellulose | |

Using the polymers described above, Liu is able to achieve very rapid dissolution times of about 1 to 40 seconds in an aqueous solution.

3. The Murray Reference

The Murray reference like, the Liu reference, teaches the need for a fast-release dosage form that quickly releases an active ingredient in the oral cavity and that does not use mammalian gelatin. Murray fills this need through the use of non-gelling, fish gelatin.

Murray uses a conventional, multi-step, lyophilization process comprising the steps shown below to produce the rapid release matrix of the Murray invention.

Murray Process

(1) Preparation of a "matrix" which consists of fish gelatin dissolved in aqueous solution;

(2) Addition of the solution of Step 1 in aliquots to containers, e.g., blister pack or glass vial;

(3) Freezing the samples and holding frozen samples for a time; and

(4) Freeze-drying the samples under pressure and the addition of heat to remove moisture.

Murray teaches that other matrix formers may be used in combination with the fish gelatin (Col. 5, lines 24-35) among which are other gelatins, dextrin's, gums, polysaccharides and synthetic polymers such as polyvinylpyrrolidone. Using the fish gelatin as a matrix former, Murray is able to get "dispersion" times of from less than a minute to 1 to 10 seconds.

Although the Murray reference describes a very broad range of active ingredients that may be formulated in the fish gelatin matrix, the reference does not describe the preparation of any dosage form containing an active agent. It is not clear from the reference if Murray obtains a "tablet" using the freeze drying process described in the reference. The "cake" left in the container after freeze drying will rapidly reconstitute upon addition of water; however, what is obtained would appear to be a liquid not a tablet.

The disclosure of the Murray reference raises more questions than it answers. Unlike the Liu reference which very clearly teaches the preparation of a rapid dissolution tablet containing a drug, Murray fails to teach the preparation of any tablet *per se*, much less one containing a drug. What Murray specifically describes is the preparation of a matrix for delivering an active agent.

C. Applicant's Invention (WO 00/67694)

The invention claimed herein is directed to a rapid dissolution tablet or solid dosage form containing an active ingredient which is made using electrohydrodynamic aerosolization/spraying means. In one embodiment of the invention, a carrier liquid comprising a biocompatible water soluble polymer and an active agent is supplied to an outlet and a charge is applied to the carrier liquid or the nozzle such that the surface tension of the liquid is overcome and fibres are formed which are attracted to a surface and which fibres deposit on the surface as a 3-dimensional mat or web of fibres. Tablets or other shapes may be cut from the mat and packages according to conventional

methods. The tablets of the invention rapidly dissolve, usually in less than 60 seconds, in the mouth when exposed to saliva or when taken with water.

The polymer used in the method of Applicant's invention must be biologically acceptable or compatible and must be hydrophilic so as to rapidly dissolve upon contact with aqueous liquid. Polymers suitable for use in Applicant's invention include: food grade gelatin, polyvinyl pyrrolidone, polyvinyl alcohol, polysucrose, starch, and cellulose. The preferred polymers for use in the methods of the invention include fish gelatin, polyvinylpyrrolidone and polyvinyl alcohol based on the stability of the fibres and solubility in water as indicated in the tables at pages 15-16 of Applicant's specification (WO 00/67694).

By use of Applicant's method the skilled artisan is able to prepare a dosage form which is inherently strong based on its 3-dimensional web of fibers as illustrated in Fig. 9 of the specification. Further, it is usually not necessary to use any organic solvents in the methods of the invention; however, even if such solvents as ethanol and acetone are used to help solubilize an active ingredient or polymer, the solvent evaporates as the fibre forms.

D. Arguments

The disclosure of the Coffee reference standing alone fails to render the claimed invention obvious because Coffee does not teach a rapid-dissolution oral dosage form, but rather a wound dressing which is bioresorbable or biodegradable and which does not rapidly dissolve upon contact with aqueous liquids. There is no disclosure in Coffee which teaches one skilled in the art anything about the preparation of a rapid-dissolution solid oral dosage form. Examiner recognizes that this is true and uses the teachings of Liu and Murray to add this teaching into the disclosure of Coffee.

Examiner asserts that the person of ordinary skill would have been motivated to make "these modifications" (using the polymers of Liu and Murray in Coffee's method) because vinylpyrrolidone-vinyl acetate copolymer and fish gelatin would assist in making tablets with (i) better resistance to moisture and (ii) have adequate hardness. The

skilled artisan would reasonably have expected success because Coffee and Liu and Murray teach a "process of manufacturing tablets that can be used in the same field of endeavor, i.e., a process that produces tablets that are advantageously hard, and dissolve rapidly in the oral cavity upon contact with saliva.

First of all, the process described by the Coffee reference produces a wound dressing not a rapid dissolution tablet. The disclosures of Coffee are not in the "same field of endeavor" as that of Liu and Murray.

Using Examiner's logic, in order to arrive at Applicant's invention one would have to look to the teachings of Coffee and be motivated by those teachings to look to the art of rapid-dissolution tablets and then incorporate those teachings back into the electrohydrodynamic methodology disclosed by Coffee. The problem with this reasoning is that there is nothing in the Coffee reference which suggests anything about the preparation of a tablet much less a rapid-dissolution tablet. Even assuming that Coffee suggested the production of an oral dosage form, the most logical next step for the skilled artisan would be to try to make tablets using the methods and materials disclosed by Coffee and this action would certainly not lead to a rapid-dissolution oral solid dosage form.

The Coffee reference teaches the use of biodegradable and bioresorbable polymers such as polylactic acid, polyhydroxybutyric acid, polyvinyl alcohol and polyglycolic acid and it is these polymers that the Coffee reference might motivate the skilled artisan to use in further research. At the time Applicant's claimed invention was made, it was well known in the art that the polymers used by Coffee were useful in the preparation of "sustained release" solid dosage forms not "rapid release". See US 5,051,261 (McGinity et al) and US 5,128,144 (Korsatko-Wabnegg et al).

The McGinity and Korsatko references describe the preparation of sustained release tablets using polylactic acid and hydroxybutyric acid polymers. McGinity specifically teaches (Col. 2, lines 33-43) that polylactic acid is well known polymer for use in preparation of sustained release tablets. The data shown in Fig. 1 to Fig. 5 of the

Korsatko reference demonstrates that skilled artisans regard sustained release as occurring over hours not seconds as is the case in a rapid release product

The polymers used in the invention of Coffee are polymers which were well known to be useful in the preparation of sustained release oral dosage forms. Assuming the skilled artisan was motivated to further research by the disclosure of Coffee, the logical direction would be in the area of sustained release.

It is respectfully contended that one skilled in this art would not have combined the teachings of Liu and Murray references with the teachings of Coffee because these references are directed to the preparation of rapid release or fast dissolution tablets and not a sustained release product. Further, neither Coffee, Liu or Murray contain any suggestion that equates the issues and methods associated with the production of a rapid dissolution oral dosage forms with the preparation of sustained release oral dosage forms.

Examiner combines the teachings of Coffee and Liu and Murray to arrive at the claimed invention. However, there is no link or nexus which would lead the skilled artisan from the teachings of Coffee to the teachings of Liu and Murray which are related to rapid dissolution (rapid release) oral dosage forms to conclude that polyvinylpyrrolidone or fish gelatin would be desirable polymers to use in the method of Coffee.

It is respectfully contended that Coffee standing alone fails to render the presently claimed invention obvious within the meaning of 35 USC §103(a) and that the skilled artisan would not have combined the teachings of Coffee with the teachings of Liu and Murray because the Coffee reference fails to provide any direction or teaching that would lead the skilled artisan to the preparation of a rapid-release tablet. The Coffee reference does teach the use of polymers which are known to be used in the preparation of sustained release tablets and that is the direction that the Coffee reference points the skilled artisan.

## III. CONCLUSION

Based on the amendments and arguments made herein, it is respectfully asserted that Examiner's rejection under 35 USC §103(a) has been overcome and that this Application is in condition for allowance. Examiner is respectfully requested to withdraw all rejections and to issue a Notice of Allowance. If there are any questions regarding these amendments and remarks, Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

By: Patricia A. Coburn

Name: Patricia A. Coburn

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Reg. No. 28,594
(614) 766-9136